

Ischemic Stroke Subtype and Presence of Sleep-disordered Breathing: The BASIC Sleep Apnea Study

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Background: Little is known about the prevalence of sleep-disordered breathing (SDB) across ischemic stroke subtypes. Given the important implications for SDB screening, we tested the association between SDB and ischemic stroke subtype in a population-based study. **Methods:** Within the Brain Attack Surveillance in Corpus Christi Project, ischemic stroke patients were offered SDB screening with the Apnea-Link Plus (n = 355). A neurologist assigned Trial of the ORG 10172 in Acute Stroke Treatment subtype (with an additional category for nonlacunar infarctions of unknown etiology) using hospital records. Unadjusted and adjusted (demographics, body mass index, National Institutes of Health Stroke Scale, diabetes, history of stroke/transient ischemic attack) logistic and linear regression models were used to test the association between subtype and SDB or apnea-hypopnea index (AHI). **Results:** Median age was 65%, and 55% were men; 59% were Mexican American. Median time from stroke onset to SDB screen was 13 days (interquartile range [IQR] 6, 21). Overall, 215 (61%) had SDB (AHI ≥ 10). Median AHI was 13 (IQR 6, 27). Prevalence of SDB by subtype was cardioembolism, 66%; large-artery atherosclerosis, 57%; small-vessel occlusion, 68%; other determined, 50%; undetermined etiology, 58%; and nonlacunar stroke of unknown etiology, 63%. Ischemic stroke subtype was not associated with SDB in unadjusted ($P = .72$) or adjusted models ($P = .91$) models. Ischemic stroke subtype was not associated with AHI in unadjusted ($P = .41$) or adjusted models ($P = .62$). **Conclusions:** In this population-based stroke

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surveillance study, ischemic stroke subtype was not associated with the presence or severity of SDB. Sleep-disordered breathing is likely to be present after ischemic stroke, and the subtype should not influence decisions about SDB screening. **Key Words:** Ischemic stroke—stroke subtype—sleep-disordered breathing—sleep apnea—epidemiology.

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Introduction

Sleep-disordered breathing (SDB) has important relevance to ischemic stroke. Not only is it highly prevalent poststroke¹ but it is also an independent risk factor for stroke²⁻⁴ and poor stroke outcomes.⁵ Although the benefits of SDB treatment in stroke patients are not currently established, simple methods to identify subgroups of stroke patients at particularly high risk would be useful for clinical and research purposes. Currently, the American Stroke Association does not provide specific guidelines about SDB screening after stroke, but acute stroke guidelines do advise careful observation and prevention of oxygen desaturations.⁶ If the prevalence of SDB differs across ischemic stroke subtypes, subtype identification may inform decisions about the need to screen for SDB. Furthermore, an association between subtype and SDB may provide insight into the pathophysiology of post-stroke SDB and its associated risk factors. We, therefore, tested the association between the presence and severity of SDB and ischemic stroke subtype in a population-based stroke study.

Materials and Methods

Subjects

Ischemic stroke patients were identified through the Brain Attack Surveillance in Corpus Christi (BASIC) project, a population-based stroke surveillance study in Nueces County, TX. Detailed methods have been previously reported.^{7,8} In summary, all cases of ischemic stroke and intracerebral hemorrhage (ICH) involving Nueces County residents with an age 45 or older are identified from each of the 7 acute care community hospitals in the county through active and passive surveillance. No academic medical centers are present in this community. Active surveillance that includes prospective review of admission logs for validated stroke symptom terms is supplemented by passive surveillance for specific *International Classification of Diseases, Ninth Revision*, codes (430-438, excluding codes 433.x0 and 434.x0 [$x = 1-9$], 437.0, 437.2, 437.3, 437.4, 437.5, 437.7, 437.8, and 438). The county is geographically isolated, which facilitates complete case capture. Study neurologists use source documentation to validate each case. Subjects who enroll in BASIC are offered sleep-disordered breathing (SDB) screening with the ApneaLink Plus device. These studies

are performed in the subjects' current venue (acute stroke hospitalization, home, etc.). Current use of supplemental oxygen, current mechanical ventilation or other positive pressure ventilation, and pregnancy are exclusionary. Subjects are offered enrollment if they meet eligibility criteria within 30 days of stroke symptom onset if identified through active surveillance and 45 days if identified through passive surveillance. Patients with ICH were excluded from analysis as this study used a classification system restricted to ischemic stroke patients and because of the small numbers of ICH patients enrolled. The University of Michigan and Corpus Christi hospital systems' Institutional Review Boards approved this project. Written informed consent was obtained from each subject or a surrogate if the patient was not able to consent for him or herself.

Ischemic Stroke Subtype and Clinical Data

For subjects who were identified as eligible for SDB assessment from September 8, 2010, to March 7, 2013, detailed records including diagnostic test results, electrocardiograms, radiology reports, admission notes, and discharge summaries were reviewed by a board-certified neurologist with stroke fellowship training, masked to age, race/ethnicity, and SDB status. Each case was classified into 1 of 5 stroke subtype categories of the Trial of the ORG 10172 in Acute Stroke Treatment (TOAST)⁹ study: large-artery atherosclerosis, cardioembolism, small-vessel occlusion, stroke of other determined etiology, and stroke of undetermined etiology.⁹ An additional category of "nonlacunar stroke of undetermined etiology" was designated for large strokes that did not have sufficient evidence to be categorized as large-artery atherosclerosis or cardioembolism, or that qualified for both, as has been used in BASIC previously.¹⁰ Information on presence or absence of a large-artery source and presence or absence of a high- or medium-risk cardioembolic source was identified, based on TOAST criteria. If sufficient tests had not been performed to exclude a large-artery source (evaluation of the relevant cervical vessels of the relevant distribution) or cardioembolic source (electrocardiogram and an echocardiogram needed if cardioembolic source not already known), this was also noted.

Information on race/ethnicity and sex were obtained through a baseline interview, and information about age, vascular risk factor data, weight, and height (for

body mass index [BMI] calculations) were ascertained from the medical record. Initial National Institutes of Health Stroke Scale (NIHSS) scores were obtained directly from the medical record or abstracted from the medical record based on standard methods.¹¹

Sleep Apnea Assessment

Sleep apnea was assessed with the ApneaLink Plus, a validated¹²⁻¹⁹ portable respiratory monitor that measures nasal pressure, oxygen saturation, pulse, and respiratory effort. Consistent with ApneaLink's default settings used in successful validation studies,^{13,16,17} an apnea was defined by 10 seconds or more of nasal pressure reduction by 80% or more of the baseline. Consistent with the American Academy of Sleep Medicine 2007 guidelines, the prevailing guidelines at this study's onset, an hypopnea was defined by 10 seconds or more of nasal pressure reduction by 30% or more, if followed by an oxygen desaturation of 4% or more (unless oximetry data were missing for a significant portion of recording, in which case it was defined by ≥ 10 seconds of nasal pressure reduction of $\geq 50\%$).²⁰ The apnea-hypopnea index (AHI, correlation between ApneaLink Plus and full polysomnography, .94)²¹ was calculated as the sum of all apneas and hypopneas averaged over the hours of the study. The central apnea index (correlation between ApneaLink Plus and full polysomnography, .97)²¹ was calculated as the number of central apneas averaged over the hours of the study. Before automated analysis by the ApneaLink Plus software, a registered polysomnographic technologist reviewed each recording to eliminate artifacts and to adjust any inappropriately scored events. SDB was defined conservatively as an AHI of 10 or more given the high sensitivity and specificity for this threshold and the overwhelming predominance of obstructive rather than central events in stroke patients.^{13,15,22}

Statistical Methods

Descriptive statistics were used to summarize demographics and baseline data. Logistic regression was used to test the association between stroke subtype and SDB, the primary outcome measure, unadjusted and adjusted for these prespecified potential confounders: age, sex, race/ethnicity, body mass index, diabetes, history of stroke/transient ischemic attack, and NIHSS. To assess the overall association between stroke subtype and SDB, a model with subtype modeled categorically as a series of 4 dummy variables (referent was small vessel) was compared with a model without the subtype variable using a likelihood ratio test ($\chi^2_{df=4}$), with and without adjustment. The association between the presence of a large-artery source (modeled categorically as yes, no, insufficient tests) and presence of a cardioembolic source (modeled categorically as high-risk source, medium-risk

source, no source, insufficient tests) and SDB were tested similarly, with no source as the referent. Linear regression was used to test the association between subtype and AHI, the secondary outcome measure, unadjusted and adjusted for the potential confounders described earlier. The natural logarithm of the AHI plus one was used instead of AHI given its skewness. Model assumptions were tested with visual inspection of appropriate residual and diagnostic plots. To assess the overall association between subtype and AHI, unadjusted and adjusted models with and without the subtype variables were compared with F tests. Subjects of American Indian race and non-Hispanic ethnicity ($n = 5$) and those with a subtype of other determined etiology ($n = 2$) were excluded from regression models because of small numbers. Analyses were performed with TIBCO Spotfire S+® 8.1 for Windows or R version 2.13.1.

Results

Of 684 ischemic stroke subjects interviewed in BASIC, 515 met eligibility criteria for SDB testing. Of the 378 (73%) who consented and had ApneaLink Plus studies performed consecutively between September 8, 2010, and March 7, 2013, 23 had insufficient ApneaLink Plus data. The remaining 355 subjects are included in this analysis. Demographic and baseline information is found in Table 1. Median time from stroke onset to ApneaLink Plus study was 13 days (interquartile range [IQR] 6, 21), with no difference by SDB status ($P = .24$). The median AHI was 13 (IQR 6, 27), and 218 (61%) had SDB. The

Table 1. Baseline characteristics of ischemic stroke subjects ($n = 355$)

Baseline characteristic	Median or n (% or IQR)
Age	65 (57, 77)
Race/ethnicity	
Non-Hispanic white	125 (35)
Hispanic	210 (59)
American Indian	5 (1)
Black	15 (4)
Male	197 (55)
Hypertension	291 (82)
Dyslipidemia	173 (49)
Prior stroke/TIA	95 (27)
Diabetes	166 (47)
Coronary artery disease	99 (28)
Atrial fibrillation	41 (12)
Current smoker	83 (23)
Former smoker	58 (16)
Excessive alcohol intake	47 (13)
NIHSS	4 (2, 7)
Body mass index	28 (25, 33)

Abbreviations: ICH, intracerebral hemorrhage; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack.

median central apnea index was .0 (IQR .0, 2.0). 70% of men had SDB (median AHI 18 [IQR 8, 32]), and 51% of women had SDB (median AHI 10 [IQR 5, 21]). Of “non-Hispanic whites”, 54% had SDB, whereas 67% of MAs had SDB. A large-artery source was identified in 51 (14%) and no large-artery source in 227 (64%), whereas the remainder ($n = 77$, 22%) had insufficient tests to exclude a large-artery source. A high-risk cardioembolic source was identified in 65 (18%), a medium-risk source in 40 (11%), no cardioembolic source in 174 (49%), and the remainder had insufficient tests to exclude a cardioembolic source ($n = 76$, 21%); 18 subjects (5%) had both a cardiac source (medium or high risk) and a large-artery source identified. Nonlacunar stroke of unknown etiology was the most common (36%) TOAST subtype identified, followed in descending order by undetermined etiology (32%), cardioembolism (18%), small-vessel occlusion (7%), large-artery atherosclerosis (6%), and other determined etiologies (1%). Distribution of TOAST subtype was similar by sex (men/women: 36%/37% nonlacunar stroke of unknown etiology, 26%/39% undetermined etiology, 21%/15% cardioembolism, 8%/6% small-vessel occlusion, 8%/4% large-artery atherosclerosis, and 1%/0% other determined etiologies; $P = .07$). Median AHI and SDB prevalences by subtype and presence of cardioembolic or large-artery source are found in Table 2.

Table 2. Prevalence and severity of sleep-disordered breathing (AHI ≥ 10) by ischemic stroke subtype and presence of large artery or cardioembolic source

Ischemic stroke subtype or presence of large artery or cardioembolic source	AHI, median (IQR)	Sleep apnea, n (%)
Stroke subtype		
Cardioembolic ($n = 64$)	16 (7, 32)	42 (66)
Large artery ($n = 23$)	13 (6, 27)	13 (57)
Small vessel ($n = 25$)	17 (7, 27)	17 (68)
Other determined ($n = 2$)	15 (12, 17)	1 (50)
Undetermined ($n = 113$)	12 (5, 22)	65 (58)
Nonlacunar of unknown etiology ($n = 128$)	15 (7, 30)	80 (63)
Large-artery source		
Yes ($n = 51$)	21 (8, 34)	36 (71)
No ($n = 227$)	12 (6, 27)	132 (58)
Insufficient tests ($n = 77$)	15 (6, 23)	50 (65)
Cardioembolic source		
High-risk source ($n = 65$)	22 (12, 35)	50 (77)
Medium-risk source ($n = 40$)	15 (7, 24)	23 (58)
No high- or medium-risk source ($n = 174$)	12 (6, 23)	100 (57)
Insufficient tests ($n = 76$)	12 (6, 32)	45 (59)

Abbreviations: AHI, apnea-hypopnea index; IQR, interquartile range.

Subtype was not associated with SDB in unadjusted ($\chi^2_{df=4}=2.0$, $P = .72$) or adjusted analysis ($\chi^2_{df=4}=1.0$, $P = .91$). Similarly, large-artery source ($\chi^2_{df=4}=2.4$, $P = .30$) and cardioembolic source ($\chi^2_{df=4}=6.5$, $P = .09$) were not associated with subtype. However, in the adjusted analysis, compared with no source, a high-risk cardiac source was associated with SDB (odds ratio [OR] 2.32, 95% confidence interval [CI]: 1.12, 4.83), whereas medium-risk source (OR .85, 95% CI: .40, 1.83) and insufficient tests (OR 1.17, 95% CI: .64, 2.14) were not. Subtype was not associated with AHI in unadjusted ($F = 1$, $P = .41$) or adjusted ($F = .67$, $P = .62$) analyses.

Discussion

This large population-based study of ischemic stroke patients shows that the prevalence of SDB is greater than 50% in all ischemic stroke subtypes, classified by the modified TOAST criteria but that subtype is not associated with either the presence of SDB or severity of SDB. Similarly, the presence of a large-artery source, irrespective of the TOAST subtype classification, is also not associated with the presence or severity of SDB. The results suggest that identification of ischemic stroke subtype or simply identification of a large-artery source should not influence the decision to screen for SDB poststroke given the high prevalence across all subtypes. Although no overall association was identified between cardioembolic source and SDB, identification of a high-risk cardioembolic source, compared with no source, was associated with the presence of SDB. Nonetheless, given the high prevalence of SDB in those with a medium-risk source and no source, practical decisions about SDB screening are unlikely to be influenced by these results.

Previous knowledge about the association between ischemic stroke subtype and SDB is limited. One prior study of only 50 subjects also showed no association between SDB (AHI ≥ 10) and TOAST subtype.²³ A second study of 90 subjects suggested that the large-artery atherosclerosis subtype was more common in subjects with an AHI of 30 or more than in those with an AHI less than 10.²⁴ Other studies that used non-TOAST classification schemes showed either no association between subtype and SDB ($n = 147$)²⁵ or a higher AHI in those with lacunar infarctions ($n = 8$) than anterior circulation cortical strokes ($n = 53$)²⁶ based on the Oxfordshire Community Stroke Project classification. Our study extends the literature through the study of this topic in a larger cohort of stroke patients and with the use of the additional TOAST subcategory of undetermined etiology for those with nonlacunar infarctions of unclear source. Unlike the previous studies, our study was also performed within a population-based stroke study in a community without an academic medical center, so referral bias was limited.

The frequency of undetermined etiologies in the present study was higher than in some other population-based studies from outside the United States,²⁷⁻³⁰ but it appears that subjects with an insufficient diagnostic evaluation are sometimes excluded from the results in other studies rather than assigned to the undetermined etiology category.³⁰ Our frequency of undetermined etiologies is more in keeping with other population-based work in the United States.^{10,31} Our high prevalence of undetermined etiologies may also be partially attributable to the presence of only community hospitals and our strict adherence to the definition of small-vessel occlusion to include only those with a presentation consistent with a classical lacunar syndrome.

The association found in the present study between a high-risk cardioembolic source and SDB may be because of a higher prevalence of SDB in those with cardiac disease. SDB has a known association with heart failure, atrial fibrillation, and coronary disease.³² We did not account for a history of cardiac conditions in our models to avoid overadjustment as these conditions are part of the definition of cardioembolic subtype.

Limitations to this study include the use of a portable respiratory monitor for the assessment of SDB rather than gold-standard polysomnography performed in a sleep laboratory. However, the device used has been well validated¹²⁻¹⁹ and is more practical than polysomnography for use in patients with recent stroke.³³ Furthermore, most research investigations of poststroke SDB do not use polysomnography.^{1,5,24,26,34,35} Stroke subtype was determined based on retrospective chart review, and some subjects were classified as an undetermined etiology because of incomplete diagnostic evaluation. This limitation is not only inherent to this type of observational work but does also result in increased generalizability of findings. Use of the TOAST criteria may have increased the proportion of undetermined etiology compared with other classifications.³⁶ Because this study included a high proportion of Mexican Americans, the results may not be generalizable to communities with a different racial/ethnic distribution. However, demographics, stroke risk factors, and stroke severity of ischemic stroke patients who participate in SDB screening are similar to the overall BASIC population, which increases the generalizability within this community. Stroke severity was low overall likely because of the population-based nature of this study performed without the referral bias of an academic medical center. Lastly, inability to review actual images, which were unavailable, as opposed to radiology reports, may have obscured infarction size in some cases and raised the frequency of undetermined etiologies.

This large study in a biethnic community shows that ischemic stroke subtype is not associated with either post-stroke SDB presence or SDB severity. Thus, ischemic

stroke subtype should not influence the decision to screen for SDB in poststroke patients. The high prevalence of SDB after stroke, in this population-based study and previous reports, suggests that systematized screening for SDB may be considered.

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